REMARKS

Claims 16-17 and 61-64 have been amended. Claims 16-17, 19-21 and 60-84 are pending.

Amendments to the Specification and Abstract

The Examiner objects to the length of the Abstract of the Disclosure. The abstract has been amended to delete lines 15-33, thereby obviating this objection. In addition, the specification has been amended to correct certain informalities.

Amendments to the Claims

Claims 16-17 and 61-64 have been amended to delete "selectively".

Claims 63 and 64 have been further amended to recite "CXC Chemokine Receptor 3 (CXCR3) protein or functional variant thereof". Support for the recitation of "functional variant" is found at page 14, line 23 *et seq.*, for example.

The amendments to the specification and claims are supported by the application as filed. Therefore, this Amendment adds no new matter.

Additional remarks addressing the rejections set forth in the Office Action are set forth below under appropriate subheadings.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 16-17, 19-21 and 60-84 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid sequence as set forth in SEQ ID NO:2, is not deemed to reasonably provide enablement for amino acid sequences that are variants of said sequence.

In his statement of rejection, the Examiner includes Claims 19-21, 60 and 69-76 as being rejected on this basis. However, independent Claims 19, 20, 21 and 60 are drawn to: an isolated human CXC Chemokine Receptor 3 (CXCR3) protein encoded by the nucleic acid illustrated in

Figure 1 (SEQ ID NO:1); an isolated human CXC Chemokine Receptor 3 (CXCR3) protein comprising an amino acid sequence as set forth in Figure 2 (SEQ ID NO:2); a fusion protein comprising a human CXC Chemokine Receptor 3 (CXCR3) protein, wherein the amino acid sequence of said CXCR3 protein is a sequence encoded by the nucleotide sequence illustrated in SEQ ID NO:1; or a fusion protein comprising a human CXC Chemokine Receptor 3 (CXCR3) protein wherein the amino acid sequence of said CXCR3 protein consists of the amino acid sequence of Figure 2 (SEQ ID NO:2), respectively. Claims 19-21 and 60 do not recite "variant", therefore the rejection should be withdrawn with respect to Claims 19-21 and 60. Claims 69-76, are also rejected on this basis, insofar as they depend on the recitation in Claims 16-17, 61-65 and 67-68 of "variant" of a CXCR3 protein. Because Claims 19-21 and 60 do not recite "variant", the rejection should also be withdrawn with respect to Claims 69-76. Withdrawal of the rejection of Claims 19-21, 60 and 69-76 is requested.

The Examiner refers to particular claims in setting forth the basis for the rejection. Applicants' further remarks addressing the rejection are presented below under appropriate subheadings.

Claims 16-17, 61-65 and 67-68

Claims 16-17, 61-65 and 67-68 are rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, there is not adequate guidance as to the nature of the variants which Applicants claim. The Examiner states that "[t]here is no guidance provided in the specification as to the relationship between the structure of CXCR3 and its function" and that "[w]ithout this information, it would require undue experimentation for one of skill in the art to generate a substantially purified CXCR3 polypeptide, other than that which is exemplified in the specification" (Office Action, page 1, last line to page 2, line 4).

The specification as filed contains sufficient teachings and guidance which enable the person of ordinary skill in the art to generate a CXCR3 polypeptide as claimed using no more than routine experimentation. For example, at page 16, lines 17-26 of their specification, Applicants teach:

> Information regarding the structure and function of mammalian G protein coupled receptors, including CXC chemokine and CC chemokine receptors, provides a basis for dividing mammalian CXCR3 proteins into functional domains (Murphy, P.M., "The molecular biology of leukocyte chemoattractant receptors," *Annu. Rev. Immunol., 12*:593-633 (1994) and Gerard, C. and N.P. Gerard, "The pro-inflammatory seven transmembrane segment receptors of the leukocyte," *Curr. Opin. Immunol., 6*:140-145 (1994), and references cited therein).

The cited articles by Murphy (Murphy, P.M., *Annu. Rev. Immunol., 12*:593-633 (1994), Reference AR, of record) and Gerard and Gerard (Gerard, C. and N.P. Gerard, *Curr. Opin. Immunol., 6*:140-145 (1994); Reference AS3 in the Supplemental Information Disclosure Statement filed concurrently herewith) clearly define structural features of leukocyte chemoattractant receptors which are involved in receptor function, including α chemokine receptors, of which CXCR3 is a member. For example, Murphy teaches that the sequence differences between three α chemokine receptors, namely IL8RA, rabIL8R and IL8RB, cluster in the proposed N-terminal segment, the e2 loop and the C-terminus (Murphy, P.M., page 613, last paragraph). Murphy further teaches that N-terminus and e3 loop may represent important domains in ligand binding for the IL8 receptors (Murphy, P.M., page 614, first paragraph). In agreement with this, Gerard and Gerard teach that "[t]he acidic nature of the amino-terminal region of the C5a and chemokine receptor complements the cationic ligands, and forms part of the ligand-binding site" (Gerard and Gerard, page 140, column 2, lines 4-7, emphasis added). Gerard and Gerard also teach that the third extracellular loop of the α chemokine receptors, IL-8 receptor A (CXCR1) and IL-8 receptor B (CXCR2), contains structures critical for ligand binding (Gerard and Gerard, page 140, column 2, lines 7-10). In addition, Murphy discusses the results of studies which investigated ligand binding specificity using chimeric receptors in which the N-terminal segments of IL8RB and rabIL8R were switched. Murphy states that the results of these N-terminal chimeric receptor studies "clearly implicate this [N-terminal] domain in determining the selectivity of the receptors for Groα and NAP-2" (Murphy, P.M., page 613, last paragraph).

Murphy and Gerard and Gerard disclose the relationship between the structure and the function of leukocyte chemoattractant receptors, and provide evidence of the importance of the N-terminal domain of α-chemokine receptors in ligand binding. Thus, the teachings of Murphy,

as well as those of Gerard and Gerard, clearly demonstrate that the person of ordinary skill in the art at the time that the invention was made knew that certain domains of chemokine receptors were critical for particular receptor functions. For example, these references clearly show that the person of ordinary skill in the art knew that the N-terminal domain of chemokine receptors (e.g., α-chemokine receptors, such as CXCR3) were involved in ligand binding.

Applicants also teach that:

> The human CXCR3 nucleic acid described herein, or sufficient portions thereof, whether isolated, recombinant and/or synthetic, including fragments produced by PCR, can be used as probes or primers to detect and/or recover nucleic acids (e.g., genomic DNA, allelic variants, cDNA) encoding CXCR3 receptors (homologs) or other related receptor genes (e.g., novel CXC chemokine receptor genes)...This can be achieved using the procedures described herein or other suitable methods, including hybridization, PCR or other suitable techniques.

Specification, at page 21, lines 3-16. Thus, Applicants provide clear teachings of how to isolate CXCR3 nucleic acids which encode CXCR3 proteins.

As noted by the Examiner, the question of enablement focuses not on whether some experimentation may be needed to practice the invention, but on whether the experimentation is undue. Thus, the appropriate test of enablement is whether the skilled person having Applicants' specification in hand would be able to practice the claimed invention without undue experimentation.

In view of the teachings disclosed in Applicants' specification, it is apparent that the person of ordinary skill in the art, with Applicants' specification in hand, could readily generate or obtain an isolated CXCR3 protein using no more than routine experimentation. The skilled person could isolate a nucleic acid encoding a CXCR3 protein and then could test the isolated CXCR3 protein for function using the methods taught in the specification (see, for example, binding and/or binding inhibition assays (page 22, lines 5-19 and page 39, line 1 *et seq.*), signalling assays (page 22, lines 20-31, page 42, line 3 *et seq.*), chemotaxis assays and/or assays measuring mediator release (page 22, line 32 to page 23, line 8 and page 44, line 3 *et seq.*)) or other suitable methods.

The specification provides additional guidance and exemplification pertinent to the preparation of variants. For example, Applicants teach that amino acids from the N-

terminal, C- terminal or internal regions of the protein can be deleted in step-wise fashion, and the resulting protein or polypeptide can be screened for function (Specification, at page 16, lines 10-26). Variants of human CXCR3 protein, "differing by the addition, deletion or substitution of one or more amino acid residues" are also described (Specification, at page 15, lines1-14). Techniques well-known to the skilled man, including site-directed mutagenesis, cassette mutagenesis or other suitable techniques can be used to prepare functional variants of human CXCR3 synthetically or recombinantly. Variant CXCR3 proteins so produced can in turn be screened for the requisite function as, for example, taught by Applicants (see e.g., Specification, at page 22, line 5 *et seq.*).

Screening isolated proteins (or host cells that express recombinant receptors) to ascertain receptor-mediated functions is considered routine in the art of receptor biology, and does not constitute undue experimentation. This routine screening is analogous to the screening of hybridomas to identify those hybridomas that produce a desired antibody which the Wands court determined was not undue experimentation. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In Wands, the court held:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody. . . Furthermore, in the monoclonal antibody art it appears that an "experiment" is not simply the screening of a single hybridoma but is rather the entire attempt to make a monoclonal antibody against a particular antigen. This process entails immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics.

Thus, the test is not simply quantitative. A considerable amount of experimentation is permissible if, as here, it is routine. Like the monoclonal antibody technology considered by the Wands court, the nature of the instant technology area is that it involves screening proteins to identify which ones possess desired characteristics. As was the case in Wands, upon consideration of the proper factors, no undue experimentation is involved.

Given the state of the art, the guidance in the specification, and detailed examples regarding how to assess polypeptides of the present invention, it would not require undue experimentation to make and use the invention as claimed.

The Examiner cites Mikayama *et al.* and Voet *et al.* as evidence that it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can alter the function of the protein. Mikayama *et al.* teach that the amino acid sequences of glycosylation-inhibiting factor (GIF) and macrophage migration inhibitory factor (MIF) differ at a single position, but that GIF does not have MIF bioactivity and that MIF does not have GIF biological activity. Voet *et al.* teach that the beta subunit of sickle-cell hemoglobin (HbS) contains a single amino acid substitution (Glu → Val) and that HbS aggregates in red blood cells causing sickling of the cells. The teaching of Mikayama *et al.* and Voet *et al.* are appreciated. However, it is noted that the HbS protein is able to bind and release oxygen, and that individuals who are heterozygous for the allele encoding HbS are resistant to malaria. Thus, the HbS variant of hemoglobin retains the oxygen-carrying function of the protein and can provide certain advantages. Nonetheless, the question of whether the claimed invention is enabled does not hinge on whether certain variant proteins are disclosed in the scientific literature as having altered biological activities relative to the corresponding wild-type proteins, but on whether the person of ordinary skill in the art could make and use the invention using no more than routine experimentation.

Evidence that the specification contains an enabling disclosure and that the person of ordinary skill in the art would be able to practice the claimed invention using no more than routine experimentation is also provided by Lu *et al.* (*Eur. J. Immunol., 29*:3804-3812 (1999)) and Soto *et al.* (*Proc. Natl. Acad. Sci. USA., 95*:8205-8210 (1998)) (References AX2 and AY2 in the Supplemental Information Disclosure Statement filed concurrently herewith). Lu *et al.* describe a study in which a nucleic acid encoding a murine CXCR3 cDNA was isolated and cloned based upon hybridization using a cDNA probe corresponding to human CXCR3 (Lu *et al.*, page 3810, column 1, first paragraph). It is noted that Lu *et al.* were successful at isolating and cloning a nucleic acid encoding

murine CXCR3 using methods that were well known in the art at the time the subject application was filed or are similar to the methods that Applicants describe in their specification (see, for example, Specification, at page 20, line 9 to page 21, line 20). Soto *et al.* describe a study in which a nucleic acid encoding murine CXCR3 was isolated and cloned, using degenerate primers and Polymerase Chain Reaction (PCR) technology (Soto *et al.*, page 8205, column 2, second paragraph and page 8206, column 2, third paragraph). Similar to Lu *et al.*, Soto *et al.* were successful at isolating and cloning a nucleic acid encoding murine CXCR3 using methods that were well known in the art at the time the subject application was filed or are similar to the methods that Applicants describe in their specification (see, for example, specification at page 21, line 3 to page 22, line 4). Given the success that Lu *et al.* and Soto *et al.* had in isolating and cloning nucleic acids encoding murine CXCR3, it is apparent that a person of ordinary skill in the art would be able to practice the claimed invention using no more than routine experimentation. It is well established that "[e]nablement is not precluded by the necessity for some experimentation such as routine screening." In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In view of the foregoing, it is clear that the subject application contains a disclosure that enables the person of skill in the art to obtain a CXC Chemokine Receptor 3 protein as claimed using no more than routine experimentation.

Claims 63-64 and 83-84

Claims 63-64 and 83-84 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2, does not reasonably provide enablement for a variant having at least 90% amino acid sequence identity to SEQ ID NO:2. In the Examiner's opinion, "[t]here is no guidance provided in the specification as to how one of ordinary skill in the art would generate a nucleic acid sequence encoding a CXCR3 polypeptide other than those exemplified in the specification" (Office Action, page 4, lines 4-6).

As described above, Applicants' specification provides extensive teachings which enable the person of ordinary skill in the art to isolate or obtain and assess the activity of a human CXCR3 protein or variant thereof. Applicants' specification also teaches that multiple protein alignment can be performed using the CLUSTAL method (Higgins, D.G. and P.M. Sharp, "Description of the method used in CLUSTAL," *Gene, 73*:237-244 (1988); Reference AT3 in the Supplemental Information Disclosure Statement filed concurrently herewith) (see Specification, at page 65, lines 20-23). Thus, to make a polypeptide having an amino acid sequence that is at least 90% identical to SEQ ID NO:2, the person of ordinary skill in the art could design an amino acid sequence and then align the sequence with SEQ ID NO:2, using the CLUSTAL method (Higgins, D.G. and P.M. Sharp, *Gene, 73*:237-244 (1988)) or other suitable method, to determine if the two sequences are at least 90% identical. A polypeptide having an amino acid sequence that is at least 90% identical to SEQ ID NO:2 could be produced using any suitable method, for example, using well-established techniques of recombinant DNA technology or synthetic chemistry, and tested for function using the methods taught in the specification or other suitable methods. As described above, the screening of isolated proteins (or host cells that express recombinant receptors) to ascertain receptor-mediated functions is considered routine in the art of receptor biology, and does not constitute undue experimentation.

In view of the foregoing, it is clear that the subject application contains a disclosure that enables the person of skill in the art to obtain a CXC Chemokine Receptor 3 protein having at least 90% amino acid sequence identity with SEQ ID NO:2 using no more than routine experimentation.

Claim 16

Claim 16 is rejected under 35 U.S.C. 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that Claim 16 is not enabled for a protein,

encoded by a nucleic acid, wherein the nucleic acid hybridizes to a second nucleic acid, and also hybridizes to the complement of the second nucleic acid.

Respectfully, Applicants' claims do not require that the protein be encoded by a nucleic acid which hybridizes to a second nucleic acid, and also hybridizes to the complement of the second nucleic acid. The claimed proteins have an amino acid sequence which can be encoded by "a nucleic acid," and Applicants' specification clearly teaches that the nucleic acid can be a single-stranded or double-stranded molecule (Specification, at page 18, lines 32 *et seq.*). In making the rejection, it appears that the Examiner has overlooked the possibility of the CXC Chemokine Receptor 3 protein being encoded by a double-stranded nucleic acid molecule. It is clear that a double-stranded nucleic acid molecule comprising a coding sequence which encodes a protein in accordance with the claims can hybridize under high stringency conditions to DNA having the sequence of Figure 1 (SEQ ID NO:1) or to the complement of the sequences shown in Figure 1 (SEQ ID NO:1).

Double-stranded nucleic acids which encode a protein are frequently used in hybridization reactions. For example, a double-stranded nucleic acid (e.g., DNA fragment) can be labeled (e.g., by nick translation), the resulting labeled nucleic acid can be boiled to separate the strands, and can then be added to a hybridization mixture. Since both strands are present, this nucleic acid probe can "hybridize" with a suitably complementary target sequence comprising either the coding or non-coding strand.

A single-stranded nucleic acid molecule comprising a coding sequence for a CXC Chemokine Receptor 3 protein as claimed can hybridize with the complement of the sequences shown in Figure 1 (SEQ ID NO:1).

In view of the foregoing, it is clear that the subject application contains a disclosure that enables the person of skill in the art to practice the invention as claimed in Claim 16.

Claim 66

The Examiner includes Claim 66 in the statement of rejection, but has not provided a basis for his conclusion that this claim is not supported by an enabling disclosure. It appears that the Examiner intended to reject Claim 66 based upon the recitation of "variant" in the claim.

As discussed above, the subject application contains a disclosure that enables the person of skill in the art to obtain a CXC Chemokine Receptor 3 protein, or a labeled CXCR3 Chemokine Receptor 3 protein, as claimed using no more than routine experimentation. Therefore, Claim 66 is enabled.

If the rejection of Claim 66 is maintained, the Examiner is requested to state the basis for the rejection and to provide Applicants with an opportunity to rebut.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 16-17, 19-21 and 60-84 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner refers to particular claims in setting forth the basis for the rejection. Applicants' remarks addressing the rejection are presented below under appropriate subheadings.

Claim 16

Claim 16 recites "high stringency", which, in the Examiner's opinion, is a conditional term that renders the claim indefinite.

The second paragraph of 35 U.S.C. § 112 requires no more than that the claims set forth and circumscribe the invention with a reasonable degree of particularity and precision. In determining if particular claims satisfy the requirement of 35 U.S.C. § 112, second paragraph, the claims language must always be analyzed in light of the teachings

of the specification and prior art as it would be interpreted by one possessing ordinary skill in the art. Therefore, a claim can be properly rejected under 35 U.S.C. § 112, second paragraph, only if one of ordinary skill in the art, having Applicants' specification and claims before him, would not be able to discern with a reasonable degree of certainty the subject matter of the claims. In re Moore and Janoski, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

The Examiner's attention is directed to page 20 of Applicants' specification which teaches that:

> Such nucleic acids can be detected and isolated by hybridization under high stringency conditions or moderate stringency conditions, for example. "High stringency conditions" and "moderate stringency conditions" are explained on pages 2.10.1-2.10.16 (see particularly 2.10.8-11) and pages 6.3.1-6 in *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, eds., Vol. 1, Suppl. 26, 1991), the teachings of which are incorporated herein by reference.

Specification, at page 20, lines 9-17. The Examiner's attention is further directed to pages 2.10.10 through 2.10.12 of Ausubel *et al.* (copies of pages 2.10.1 through 2.10.16 are provided with the Supplemental Information Disclosure Statement being filed concurrently herewith as Reference AZ2) where moderate stringency and high stringency hybridization conditions are discussed, and to page 2.10.3 (paragraphs 8-10) where exemplary low stringency, moderate stringency and high stringency hybridization conditions are disclosed.

The Examiner's attention is also directed to the specification, at page 63, line 32 to page 64, line 11, which discloses the following exemplary hybridization conditions:

> For plaque hybridization screening, about 4 x 10^5 clones were transferred onto Biodyne nylon membranes (PALL AG, Muttenz, Switzerland) and probed with 2MLC22 which had been labeled to a specific activity of 1 x 10^9 dpm/μg DNA using the high prime DNA labeling kit (Boehringer Mannheim, Mannheim, Germany). Hybridization was carried out in 50% formamide, 6X SSC, 0.5% SDS, 100 μg/ml denatured salmon sperm DNA at 42°C for 20 hours using 1 x 10^6 dpm 2MLC22/ml hybridization solution. The membranes were washed once in 2X SSC, 0.1% SDS at room temperature for 10 minutes, twice in 1X SSC, 0.1% SDS at 65°C for 30 minutes, and finally once in 0.5X SSC, 0.1% SDS at 65°C for 10 minutes. Twenty-three clones were isolated from hybridization positive lambda plaques following the high stringency washes.

Specification, page 63, line 32 to page 64, line 11, emphasis added. Thus, it is clear that one of ordinary skill in the art, having Applicants' specification and claims before him, would be able to discern with a reasonable degree of certainty the subject matter of Claim 16.

Claim 16 is also rejected under 35 U.S.C. § 112, second paragraph, as being vague and indefinite because, in the Examiner's opinion, it is unclear how a nucleic acid could hybridize to both a second nucleic acid, as well as to a sequence complementary to the second nucleic acid.

As described above, Applicants claims do not require that the protein be encoded by a nucleic acid which hybridizes to a second nucleic acid, and also hybridizes to the complement of the second nucleic acid. Furthermore, as discussed above, it would be clear to the person of skill in the art that the claimed protein can be encoded by a nucleic acid molecule (a double-stranded or a single-stranded molecule) that can hybridize under high stringency conditions to DNA having the sequence of Figure 1 (SEQ ID NO:1) or to the complement of the sequences shown in Figure 1 (SEQ ID NO:1). Thus, Claim 16 is not vague and indefinite as suggested by the Examiner.

In view of the foregoing, it is clear that Claim 16 particularly points out and distinctly claims the subject matter which Applicants regard as their invention, because one of ordinary skill in the art, having Applicants' specification and claims before him, would be able to discern with a reasonable degree of certainty the subject matter of Claim 16.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 16-17 and 61-64

Claims 16-17 and 61-64 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In the Examiner's opinion, the term "selectively" in Claims 16-17 and 61-64 is a relative term which renders the claims indefinite. Claims 16-17 and 61-64 have been amended to delete the word "selectively", thereby obviating the rejection on this basis.

Rejection of Claims 16-17, 19-21 and 60-84 Under 35 U.S.C. § 102(a)

Claims 16-17, 19-21 and 60-84 are rejected under 35 U.S.C. § 102(a) as being anticipated by Marchese *et al.* (1995)(Reference AS, of record). According to the Examiner, the nucleic acid sequence disclosed in Marchese *et al.* as "GPR9 is 71.1% homologous to the polynucleotide sequence set forth in SEQ ID NO:1" and "GPR9 is disclosed as able to bind chemokines" (Office Action, page 6, third paragraph). The Examiner also states that "[t]he amino acid sequence disclosed in Marchese *et al.* has 100% amino acid identity to the amino acid sequence set forth in SEQ ID NO:2 of the instant application" and that "[s]ince the structures of the proteins are identical, it would be an inherent property of the protein disclosed in Marchese *et al.* to bind IP-10 and Mig" (Office Action, page 6, lines 21-23 and page 7, lines 3-5).

Marchese *et al.* disclose the deduced amino acid sequences of three polypeptides that are purported to be G protein-coupled receptors. One of the amino acid sequences is deduced from the nucleic acid sequence of a partial human genomic clone designated GPR9. Marchese *et al.* also teach that the gene corresponding to the partial genomic GPR9 clone has 38% identity with the IL-8 type B receptor (IL-8RB), and when conserved residues are considered, 53% similarity to IL-8RB (Marchese *et al.*, paragraph bridging pages 339-340).

The Examiner states that nucleotide sequence of GPR9 is 71.1% homologous to the polynucleotide sequence set forth in SEQ ID NO:1. The Examiner also states that "GPR9 is disclosed as able to bind chemokines" (Office Action at page 6, line 18). However, in contrast to the Examiner's statement, Marchese *et al.* do not disclose that GPR9 is able to bind chemokines. Marchese *et al.* only speculate, based on sequence homology with IL-8 receptors and the GPR2

orphan receptor, that "GPR9 may therefore represent a novel receptor belonging to the family of chemokine receptors with a role in immune responses in the body" (Marchese *et al.*, page 335, column 2, second paragraph) (emphasis added). It is well known in the art, that sequence similarity is not necessarily a reliable indicator of function. For example, one of the IL-8 receptor isotypes exhibited 69% amino acid identity with a protein reported to be an N-formyl peptide receptor from rabbit neutrophils (see Murphy, P.M. and H.L. Tiffany, *Science, 253*:1280-1283 (1991), abstract) (Reference AR3 in the Supplemental Information Disclosure Statement filed concurrently herewith). N-formyl peptides are classical oligopeptide chemoattractants and are distinguished from chemokines which are members of a distinct family of conserved proteins. Evidently aware of the limits of sequence homology in assigning function, Marchese *et al.* only speculate that "[t]he GPR9-encoded receptor may represent yet another chemokine receptor with a potential role in inflammatory and immune responses in the body," and propose that "[f]uture studies will involve binding assays to test which chemokines are functional ligands for the receptor encoded by GPR9" (see Marchese *et al.*, page 340, first full paragraph) (emphasis added). Thus, in contrast to the Examiner's assertion, Marchese *et al.* do not teach that the GPR9 polypeptide is able to bind one or more chemokines and thereby mediate cellular signalling and/or a cellular response.

The Examiner also states that "[t]he amino acid sequence disclosed in Marchese *et al.* has 100% amino acid identity to the amino acid sequence set forth in SEQ ID NO:2 of the instant application" and therefore "it would be an inherent property of the protein disclosed in Marchese *et al.* to bind IP-10 and Mig" (Office Action, page 6, lines 21-23 and page 7, lines 3-5) . In support of this position, the Examiner provides Sequence Comparison B showing 100% amino acid identity between SEQ ID NO:2 and a sequence that is purported to be the amino acid sequence of the GPR9 polypeptide disclosed by Marchese *et al.* It is not clear what sequence is compared to SEQ ID NO:2 in Sequence Comparison B, because even a cursory examination of the deduced amino acid sequence of GPR9 that is disclosed by Marchese *et al.* (see, Marchese *et al.* at FIG. 1A) reveals that the GPR9 amino acid sequence does not include an initiation methionine and lacks the four N-terminal amino acids of SEQ ID NO:2. Therefore, at the time the present invention was made, it was unknown if the partial genomic clone disclosed by

Marchese *et al.* as GPR9 was in fact part of an open reading frame (ORF), and if so, how much of the partial genomic clone was missing. Indeed, the lack of an initiation methionine in the GPR9 partial genomic sequence led Marchese *et al.* to speculate that an unknown N-terminal second exon existed. It was certainly unclear from the teachings of Marchese *et al.* whether the partial GPR9 genomic clone which was isolated could be successfully assessed for ligand binding specificity or whether the missing portion, if one existed, was required for binding specificity. As described above, the person of skill in the art at the time the invention was made knew that the N-terminal acidic domain of chemokine receptors, including α-chemokine receptors, are highly divergent and are important for ligand binding.

Because the sequence of the GPR9 polypeptide and SEQ ID NO:2 are different in the N-terminal domain, and the person of ordinary skill in the art at the time the invention was made knew that the N-terminal domain of chemokine receptors are important for ligand binding, there is no basis to conclude that the GPR9 polypeptide would inherently bind IP-10 and Mig.

The Examiner is reminded that a claim is anticipated only if every element of the claim is either expressly or inherently described in a single prior art reference. Where a claimed element is considered by the Examiner to be inherent, the element must "necessarily be present in the thing described in the reference" and be recognized by the person of ordinary skill in the art. In re Robertson, 169 F.3d 743, 49 U.S.P.Q.2d. 1942, 1950-51 (Fed. Cir. 1999). "Inherency , however, may not be established by probabilities or possibilities." In re Oelrich and Divigard, 212 U.S.P.Q. 323, 326 (CCPA 1981).

The Examiner also rejected Claims 63 and 64 under 35 U.S.C. 102(a) as being anticipated by Marchese *et al.* Claims 63 and 64 specify that the CXCR3 protein or variant comprises the extracellular N-terminal segment of the protein shown in Figure 2 (SEQ ID NO:2). As discussed above, the deduced amino acid sequence of the polypeptide encoded GPR9 genomic clone disclosed in Marchese *et al.* (see Figure 1A, at page 337) does not include the N-terminal segment of SEQ ID NO:2. Accordingly, Claims 63 and 64 are not anticipated.

The Examiner further states that Claims 60-62 and 64, and dependent Claims 65-84 are anticipated by the amino acid sequence disclosed in Marchese *et al.* as GPR14, due to the recitation of "variant". The Examiner states that GPR14 is disclosed and containing 386 amino acids while SEQ ID NO:2 is 368 amino acids long. It appears that the Examiner believes that GRP14 is a variant of SEQ ID NO:2 that includes an 18 amino acid epitope tag.

Marchese *et al.* disclose a deduced amino acid sequence of a human genomic clone referred to as GPR14. Marchese *et al.* state that "[t]he receptor encoded by GPR14 shared highest amino acid identity with the somatostatin and opioid receptors" (at page 340, right column, line 5 *et seq.*). There is no teaching that GPR14 is a chemokine receptor or has significant amino acid sequence identity to any known chemokine receptor. Accordingly, Marchese *et al.* contains no explicit or implied teaching that GPR14 can bind one or more chemokines and mediate cellular signalling and/or a cellular response in response thereto.

As discussed above, Claim 60 is drawn to a fusion protein comprising a human CXC Chemokine Receptor 3 (CXCR3) protein wherein the amino acid sequence of said CXCR3 protein consists of the amino acid sequence of Figure 2 (SEQ ID NO:2). Thus, Claim 60 does not recite "variant" of CXCR3, as suggested by the Examiner, and is not anticipated.

Claims 61 and 64 are drawn to fusion proteins comprising a human CXC Chemokine Receptor 3 protein or functional variant thereof. However, these claims define the variant as a protein that "can bind one or more chemokines and can mediated cellular signalling and/or a cellular response in response thereto," or as a protein that "can bind one or more chemokines selected from the group consisting of IP-10 and Mig and mediate cellular signalling and/or a cellular response in response thereto." As stated above, Marchese *et al.* contains no explicit or implied teaching that GPR14 can bind one or more chemokines and mediate cellular signalling and/or a cellular response in response thereto. Furthermore, Claim 64 specifies that the fusion protein comprise a CXCR3 protein or variant that comprises the extracellular N-terminal segment of SEQ ID NO:2 which is distinct from the N-terminal region of the amino acid sequence disclosed in Marchese *et al.* as GPR14. Accordingly, Claim 61 and dependent Claims 62 and 77-80, and Claim 64 and dependent Claims 83 and 84 are not anticipated by Marchese *et al.*

Additionally, as discussed above, Claims 19, 20, 21 and 60 do not recite "variant" of CXCR3 protein. Accordingly, Claims 69-76 which depend from Claim 19, 20, 21 or 60 do not read on the amino acid sequence disclosed in Marchese *et al.* as GPR14, and are not anticipated.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement is being filed concurrently herewith. Acknowledgment of consideration of the information provided in the Supplemental Information Disclosure Statement is respectfully requested in the next Office Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned or Helen E. Wendler, Esq. at (781) 861-6240.

Respectfully submitted,

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